November 15, 2002

Dr. Anne P. LeHuray
Technical Contact
The American Chemistry Council's Rubber and Plastic
Additives Panel
1300 Wilson Boulevard
Arlington, VA 22209

Dear Dr. LeHuray:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for the Substituted p-Phenylenediamines Category posted on the ChemRTK HPV Challenge Program Web site on January 17, 2002. I commend The American Chemistry Council's Rubber and Plastic Additives Panel for their commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed Comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that The American Chemistry Council's Rubber and Plastic Additives Panel advise the Agency, within 90 days of this posting on the Web site, of any modifications to its submission.

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-564-7649. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

-S-

Oscar Hernandez, Director
Risk Assessment Division

Enclosure

cc: C. Auer
A. Abramson
W. Penberthy
M. E. Weber

EPA Comments on Chemical RTK HPV Challenge Submission:
Substituted p-Phenylenediamines

SUMMARY OF EPA COMMENTS

The sponsor, the Rubber and Plastic Additives (RAPA) Panel of the American Chemistry Council, submitted a test plan and robust summaries to EPA for the p-Phenylenediamines Category dated December 13, 2001. EPA posted the submission on the ChemRTK HPV Challenge Web site on January 17, 2002. The category consists of N,N'-di-*sec*-butyl-*p*-phenylenediamine, N,N'-bis(1,4-dimethylpentyl)-*p*-phenylenediamine, 1,4-benzenediamine, N,N'-mixed phenyl and tolyl derivatives, N-(1,4-dimethylpentyl)-N'-phenyl- *p*-phenylenediamine, and N-(1-methylheptyl)-N'-phenyl-*p*-phenylenediamine.

EPA has reviewed this submission and has reached the following conclusions:

1. Category Justification. The submitter's support for grouping the chemicals in this category with regard to toxicological properties is acceptable.

2. Physicochemical Properties and Environmental Fate. (a) A vapor pressure test needs to be conducted for N,N'-di-*sec*-butyl-*p*-phenylenediamine. (b) A biodegradation study needs to be conducted for N,N'-di-*sec*-butyl-*p*-phenylenediamine. (c) The submitter needs to address deficiencies in robust summaries for water solubility.

3. Health Effects. EPA reserves judgment on the adequacy of the submitted toxicity data pending receipt of additional information in the robust summaries.

4. Ecological Effects. EPA reserves judgment on the adequacy of the submitted toxicity data on fish, daphnia, and green algae, pending adequate explanation of test conditions (addressing deficiencies in the robust summaries) and degradation products (see item 5 below) for these studies.

5. Other issues. The submitter did not discuss essential information about environmental fate provided in one robust summary that also is a critical factor in the fate and ecotoxicity evaluation of all category members. Appropriate discussion of these areas needs to be added to the test plan.

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission.

EPA COMMENTS ON THE SUBSTITUTED p-PHENYLENEDIAMINES CHALLENGE SUBMISSION

Category Definition

The submitter proposed a category defined as *p*-phenylenediamines covering five chemicals containing amino groups, which are each substituted with one alkyl or phenyl group. The submitter has subdivided the category into two groups: 1) N–alkyl substituents (N-Alkylated *p*-Phenylenediamines), and 2) N-aryl or mixed N-aryl/N-alkyl substituents (4-Aminodiphenylamine Derivatives). The N-Alkylated *p*-Phenylenediamine subcategory includes N,N'-di-*sec*-butyl-*p*-phenylenediamine (CAS no. 101-96-2) and N,N'-bis(1,4-dimethylpentyl)-*p*-phenylenediamine (CAS no. 3081-14-9) and the 4-Aminodiphenylamine Derivatives subcategory includes N,N'-mixed phenyl and tolyl derivatives of 1,4-benzenediamine (CAS no. 68953-84-4); N-(1,4-dimethylpentyl)-N'-phenyl- *p*-phenylenediamine (CAS no. 3081-01-4); and N-(1-methylheptyl)-N'-phenyl-*p*-phenylenediamine (CAS no. 15233-47-3). In addition, the submitter included supporting data on two non-category chemicals sponsored in the OECD SIDS program: N-isopropyl-N'-phenyl-*p*-phenylenediamine (CAS no. 101-72-4) and N-(1,3-dimethylbutyl)-N'-phenyl-*p*-phenylenediamine

(CAS no. 793-24-8).

Category Justification

The submitter's justification for the category is based on the structural similarity of the substances and an expectation of similar physicochemical, environmental, and toxicological properties among the members. To further refine the comparison of the properties of the members, the submitter has subdivided the category into two groups to better match the classes of substituent groups. One subgroup (alkylated –PPD) contains compounds with alkyl substituents only; the other subgroup (4-aminodiphenylamine derivatives) contains either a mixture of alkyl/aryl or aryl only substituents. The submitter has provided a rationale to demonstrate similarities between the members of each subgroup for each endpoint. For the environmentally important physicochemical endpoints, ecotoxicity endpoints, and health effects endpoints, the submitter has provided sufficient data to establish a pattern for both subgroups where the values are reasonably similar.

From the standpoint of physicochemical properties, the values for two of the endpoints (*e.g.,* water solubility and octanol/water partition coefficient) are reasonably similar among the members in each subgroup. For the vapor pressure endpoint, the compounds have been shown to have low vapor pressures (with the exception of CAS No. 101-96-2, whose value is larger than expected based on both its structure and a comparison to the value reported for the other member of the alkylated N-PPD subgroup). The data for the physicochemical endpoints support the category.

The submitter demonstrates a reasonable consistency in the values of the members for the hydrolysis and photodegradation endpoints. In addition, all tested members of the category show low or virtually no biodegradation. However, important chemical fate information was omitted from the category discussion and needs to be added (see comments below under Environmental Fate).

Finally, the available environmental fate data have many illuminating consistencies across endpoints that need to be fully coordinated and discussed in the final category analysis required of the submitter.

Test Plan

Chemistry (melting point, boiling point, vapor pressure, partition coefficient, and water solubility)

Vapor Pressure. A test needs to be conducted for CAS No. 101-96-2. The submitted vapor pressure differs substantially from estimated values; the measurement was not in accord with OECD TG 104; and the estimated value is in the range where a measured value is necessary.

Environmental Fate (photodegradation, stability in Water, biodegradation, fugacity)

In the robust summary for the third stability in water study for N-(1,3-dimethylbutyl)-N'-phenyl-*p*-phenylenediamine, the submitter provided a useful discussion of the fate of this type of substance in the presence of oxygen and water. The discussion is essential to evaluating all fate and ecotoxicity endpoints, and should have been included and expanded upon in the test plan discussion of these and any other relevant endpoints and studies.

Biodegradation. A ready biodegradation test needs to be conducted for CAS No. 101-96-2. While in general the compounds in this category do not appear to biodegrade, CAS No. 3081-14-9 did show partial degradation in an inherent test. CAS No. 101-96-2 is a simpler compound with less branching and shorter carbon side chains and so has an even greater potential for biodegradation.

Stability in water. Evaluation of this endpoint is impeded because of inaccuracies in the robust summaries

related to identification of degradation products, which need to be corrected (see Specific Comments on Robust Summaries).

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity).

Pending submission of more complete information on the identity of the test substances and other important details in the robust summaries, EPA reserves judgement on the adequacy of these endpoints.

Acute Toxicity. There is a discrepancy between the LD_{50} values listed in the test plan and those in the robust summary. The acute oral LD_{50}s listed in Table 5 of the test plan are incorrect for CAS No. 793-24-8 (the listed value of >5000 mg/kg should be $2500 mg/kg) and CAS No. 3081-01-4 (the listed value of >2000 mg/kg should be 2100 mg/kg).

Ecological Effects (fish, invertebrates, and algae).

EPA reserves judgment on the adequacy of the submitted toxicity data on fish, daphnia, and green algae, pending adequate explanation on test conditions for these studies. The submitter needs to address deficiencies in the robust summaries to allow determination of data adequacy. Because these chemicals undergo rapid degradation (hydrolysis half-life 3 to 5 hours, photolysis (one example) half-life 2 hours), the test organisms will be exposed primarily to degradation products and the latter need to be properly identified and explained (see comments under Environmental Fate).

Specific Comments on Robust Summaries

General Comment

One set of robust summaries is labeled with CAS No. 3081-14-9 and chemical name *"p*-phenylene-diamine, N-1,4-dimethylpentyl-N'-phenyl"; the number and name do not match. The submitter needs to match all of the information in this data set to the appropriate chemical.

Physicochemical Properties

Water Solubility. The robust summary is inadequate for CAS No. 101-96-2. The value provided does not agree with model estimates or the water solubility values reported for N,N'-bis(1,4-dimethylpentyl)-p-phenylenediamine (a structurally similar compound, but with longer alkyl side chains). In addition, a quantitative value should be reported for CAS No. 15233-47-3. Finally, according to robust summaries submitted by the sponsor, the water solubility in Table 2 of the test plan appears to be incorrect for CAS No. 3081-01-4 (the listed units of g/L should be mg/L).

Environmental Fate

The submitter needs to provide clarification on the degradation products. For example, the submitter indicates in two cases that one of the hydrolysis products is "4-hydroxylamine," an obvious misnomer. A degradation product listed for CAS No. 3081-14-9 is not a possible degradation product of that substance but is consistent with the title chemical name (see General Comment above).

Health Effects

General Comments. Several robust summaries were missing important details, as discussed in the sections below. In addition, in the IUCLID data sets for CAS No. 68953-84-4, the submitter did not provide sections 1.1-1.4; however, many robust summaries for this chemical refer to these sections for the identity of the test substance. Furthermore, summaries for several chemicals provided only the

commercial name of the products.

Acute Toxicity. Experimental details missing from some study summaries include sex, strain, group sizes, vehicle, test doses/concentrations, nature of the atmosphere in inhalation studies (gas, particulate, etc.), mortality-dose response, clinical signs, necropsy findings, and LD_{50}/LC_{50} confidence limits.

Repeated-Dose Toxicity. Experimental details missing from the study summaries include incidence data, magnitude of effects, and statistical significance of observed effects. Also, the NOEL and LOEL values appear to be transposed in the summary for CAS No. 3081-01-4. Finally, no NOAEL or LOAEL values were reported in the first summary for CAS No. 793-24-8.

Genetic Toxicity. The robust summary of the OECD Guideline 476 study for CAS No. 101-96-2 need to be clarified. The summary remarks refer to chromosomal aberrations, but the study type is described as a forward gene mutation assay. In addition, experimental details missing from some robust summaries include test concentrations, the use of positive and negative controls, number of replicates, and statistical analyses.

Reproductive Toxicity. Experimental details missing from the study summaries include incidence data, magnitude of effects, and statistical significance of observed effects. In the three generation study for CAS No. 793-24-8, it appears that the parental NOAEL should be 100 ppm (not 10 ppm).

Developmental Toxicity. In the study summaries, adverse effects are sometimes reported without incidence data, magnitude, or any indication of statistical significance. The first developmental study for CAS No. 68953-84-4 indicated a linear trend in decreasing fetal body weights with dose; it may be appropriate to derive a fetal toxicity NOAEL based on these effects. In the developmental toxicity study summary of CAS No. 101-72-4, 62.5 mg/kg/day is indicated as a developmental toxicity NOEL, but there was a statistically significant increase in incomplete ossification of more than one cranial bone at this dose. There was also a statistically-significant increase in incomplete ossification of more than one facial bone at 12.5 mg/kg/day. The submitter needs to address this apparent inconsistency regarding the developmental toxicity NOEL.

Ecological Effects

In general, the robust summaries did not provide enough detail. The submitter should consult EPA guidance documents for the preparation of robust summaries (http://www.epa.gov/opptintr/chemrtk/guidocs.htm). Commonly missing information included test substance purity, tested concentrations, number of organisms (or algal cultures) per concentration, solvent and negative control use and response, solvent concentration, complete mortality and/or response data, statistical methods used, test type, and water chemistry parameters. In addition, the submitter needs to provide accurate information on degradation products.

Followup Activity

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission.